LETTERS TO THE EDITOR

Ulcerative colitis is more strongly linked to chromosome 12 than Crohn's disease

EDITOR,—Lesage and colleagues reported failure to detect linkage to the IBD2 locus on chromosome 12 in a panel of 95 families with two or more relatives affected by Crohn's disease, and offered some possible explanations (*Gut* 2000;**47**:787–91). Linkage of inflammatory bowel disease (IBD) to this region was first detected in a panel of 160 families containing multiple cases of Crohn's disease, ulcerative colitis, or both.[1] Lesage *et al* justify the study of Crohn's disease families alone on the grounds that "genetic heterogeneity in susceptibility cannot be ruled out", and they imply that studying the Crohn's disease subgroup of IBD should thus maximise their chance of successful replication. We concur entirely that genetic heterogeneity is important, and we have recently reported strong evidence that it does indeed apply to chromosome 12.[2] However, our study of 367 multiply affected families suggested a significantly stronger contribution of this locus to ulcerative colitis than Crohn's disease.[2] The difference between the linkage results for ulcerative colitis (LOD=3.91) and Crohn's disease (LOD=1.66) reached statistical significance in two separate tests for heterogeneity. In the light of these results, the validity of the exclusion map drawn by Lesage *et al* is undermined. The exclusion map was based on an assumed locus specific λ_s of 2.0, but this value was derived from a panel containing Crohn's disease, ulcerative colitis, and mixed pairs.[1] Given the evidence for a substantially stronger contribution to ulcerative colitis than Crohn's disease, it is likely that the true λ_s value for this locus with regard to Crohn's disease is much less than 2. Thus the contention that Lesage *et al* can exclude a contribution of IBD2 to Crohn's disease susceptibility is probably not valid. As pointed out in the accompanying editorial, simulation studies have demonstrated that lod scores can be expected to vary, particularly when the study population is relatively small.[3] Furthermore, the implication that a panel of 157 affected relative pairs should provide sufficient power to detect linkage if this locus is contributing to disease susceptibility is at marked variance with the power calculations derived by Suarez *et al*, Mandal *et al*, and others.[4 5]

In many respects, the surprising feature is that IBD2 has been replicated in as many as five independent panels.[3] The datasets that have failed to detect linkage at this locus have all contained predominantly or exclusively Crohn's disease pairs.[6–8] Although IBD2 probably does contribute to Crohn's disease susceptibility, the effect is likely to be weak and thus would require very large panels of multiply affected families to have a realistic expectation of replicating (or excluding) the linkage result.

It is our view that attempts at fine mapping IBD2 probably have the greatest chance of success if they concentrate on panels of families and individuals with ulcerative colitis, which appears to be significantly more strongly linked to this locus than Crohn's disease.

M PARKES
J SATSANGI
D P JEWELL
Gastroenterology Unit, Radcliffe Infirmary, Oxford, UK

D E WEEKS
M M BARMADA
Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

R H DUERR
Department of Medicine and Center for Genomic Sciences, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence to: M Parkes.
miles.parkes@well.ox.ac.uk

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Reply

EDITOR,—In 1996, Satsangi *et al* reported a positive linkage between inflammatory bowel disease (IBD) multiplex families (including Crohn's disease (CD), ulcerative colitis (UC) and mixed families) with a locus (called IBD2) located on chromosome 12.[1] The attributable risk in siblings (λs) of this IBD2 locus was calculated to be 2.[1] In a recently published study in the journal, we failed to demonstrate a positive linkage on chromosome 12 using an independent panel of 95 CD multiplex families (*Gut* 2000;**47**:787–91). This result was different to the previous report and we proposed several explanations for the observed discrepancy.

The first explanation may be lack of statistical power in our replication study. We investigated a similar number of affected relative pairs (n=157, all CD pairs) compared with the first linkage analysis (n=186, 81 CD pairs, 64 UC pairs, and 41 mixed pairs). Because linkage tests may exhibit large fluctuations when applied to family sets of similar size for complex genetic disorders,[2] we tested if a gene with a λ_s risk of 2 was compatible with our observation and we were able to reject this hypothesis. We thus concluded that genetic heterogeneity may occur in Caucasian family panels for IBD susceptibility.

Parkes *et al* have recently demonstrated that this genetic heterogeneity may be related to phenotypic heterogeneity.[3] In their proposed susceptibility model, UC is more tightly linked to IBD2 than CD. This study confirms our conclusion that there is genetic heterogeneity in familial IBD. As expected, this heterogeneity may be in part reduced by an accurate phenotypic classification. Thus from a methodological point of view, Parkes' report demonstrates that working on homogeneous phenotypic groups may be preferable than pooling several phenotypes for linkage studies. Considering CD and UC families as separate subgroups, Parkes *et al* suggested that the IBD2 locus has only a marginal role in CD susceptibility. This conclusion is in complete accordance with our demonstration that the relative risk attributable to IBD2 in CD multiplex families is low.

In practice, it is difficult to know what is the weight of this IBD2 locus in both CD and UC. A line of evidence, including the above mentioned reports,[3] and a large collaborative work performed on more that 600 multiplex IBD families[4] clearly suggests that the role of the IBD2 locus is weak in CD families. In contrast, its role in UC is difficult to estimate to date. In their recent work, Parkes *et al* pooled previously investigated families from UK and US panels.[1 5] Because these families were a priori known to be positively linked to IBD2, this study provides a biased estimate of the risk attributable to *IBD2*. Thus additional works using unselected family panels are required to answer this question.

Interestingly, the IBD1 locus[6] has been postulated to play a major role in CD and to be less important in UC families. Thus it would be postulated that IBD1 is a CD susceptibility locus and IBD2 is a UC gene. Some truth may reside in this assertion. However, a line of evidence including analysis of mixed families[7] suggests that CD and UC have common familial risk factors and does not allow a simple dichotomic classification of UC and CD genes. Many additional steps, including gene identification, are now required before we can understand the underlying genetic model for IBD which will certainly be confirmed as a complex genetic disorder.

S LESAGE
H ZOUALI
J P HUGOT
Fondation Jean Dausset CEPH, 27, rue Juliette Dodu, 75010 Paris, France

Correspondence to: J P Hugot. hugot@cephb.fr

1 Satsangi J, Parkes M, Louis E, *et al.* Two stage genome-wide search in inflammatory bowel disease provides evidence for susceptibility loci on chromosomes 3, 7 and 12. *Nat Genet* 1996;**14**:199–202.
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Intestinal permeability: the cellobiose/mannitol test

EDITOR,—I should like to bring to your attention a conceptual error in the paper by Daniele *et al* (*Gut* 2001;**48**:28–33) regarding the cellobiose/mannitol test. The authors suggest that improvement in the cellobiose/mannitol ratio reflects improvement in permeability from the use of oral glutamine. However, only mannitol excretion improved significantly with glutamine; cellobiose excretion remained unchanged. As the authors explain in their methods section, it is the increased cellobiose excretion that reflects increased permeability, not the decrement in mannitol excretion. Therefore, modifications in sugar transport induced by 5-fluorouracil (5-FU) reflected only an absorptive, not a permeability, defect. The decrement in mannitol excretion parallels the decrement in D-xylose excretion, probably reflecting decreased transcellular passage of the test sugars induced by 5-FU and improved with glutamine.

R M CRAIG
Department of Gastroenterology and Hepatology, Northwestern University, Chicago, Illinois 60611, USA
r-craig@northwestern.edu

Reply

EDITOR,—I thank Dr Craig for raising this issue but I do not see any conceptual error. The apparent inconsistency that he points out in our paper (*Gut* 2001;**48**:28–33) is due to the controversy surrounding transcellular permeation of mannitol, as well as of other monosaccharides.[1] While transcellular permeation of mannitol is well known, its use for osmotic shrinkage of membrane vescicles[2] and as an extracellular fluid volume marker suggests that, at least in part, mannitol diffuses through the intercellular tight junctions. Thus it seems justified talking of permeability for mannitol. One of the reasons for its use in combination with cellobiose is the different molecular sizes of the two probes: the smaller size of mannitol allows its passage through the small tight junctions of the villi while the larger cellobiose passes through the larger tight junctions of the crypts.

Finally, we did find an increase in cellobiose excretion after fluorouracil (5-FU) that was in part prevented by oral glutamine. Although this difference did not reach statistical significance, overall the data indicate increased intestinal permeability after 5-FU, partially prevented by oral glutamine.

B DANIELE
Divisione Di Oncologia Medica B, Istituto Nazionale Tumori, via M Semmola, 80131 Napoli, Italy
bdaniele@sirio-oncology.it

1 Bjarnason I, Macpherson AJ, Hollander D. Intestinal permeability: an overview. *Gastroenterology* 1995;**108**:1566–81.
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Evaluation of the role of CFTR in alcohol related pancreatic disease

EDITOR,—In up to 30% of patients with idiopathic pancreatitis (IP) a mutation of at least one or both alleles of the cystic fibrosis transmembrane conductance regulator (CFTR) gene can be identified.[1–3] The study by Malats *et al* (*Gut* 2001;**48**:70–4) addressed the question of whether CFTR mutations, possibly together with environmental factors such as alcohol, may be associated with chronic pancreatitis or pancreatic cancer. The vast majority of the pancreatic patients (86.4%) investigated by Malats *et al* were diagnosed as having alcoholic pancreatitis (AP), and 75.4% of the cancer patients were daily drinkers. The authors found no statistically significant difference in the prevalence of delta-F508 (0%; 2.4%) and the 5T allele (10.5%; 5.5%) in the AP or cancer groups compared with the expected prevalence in the general population. The lack of a positive association of both delta-F508 and the 5T allele with AP is neither surprising nor argues against involvement of CFTR variations in the development of AP, considering the following.

In cystic fibrosis (CF), the degree of correlation between CFTR genotype and CF phenotype varies between clinical components but is highest for pancreatic involvement.[4] CFTR mutations can simplify be divided into "severe" and "mild" with respect to the degree to which mutations impair CFTR function.[5] Approximately 85% of CF patients suffer from pancreatic insufficiency (PI) while ~15% are pancreatic sufficient (PS). Generally patients with PI carry two "severe" mutations whereas PS is associated with at least one "mild" mutation (fig 1). In CF, pancreatitis is seen rather frequently in PS patients but not in PI patients. Today, more than 850 CF mutations have been reported to the CF Consortium (http\www.genet.sickkids.on.ca/cftr). The deletion delta-F508, accounting for about 70% of mutant CF alleles worldwide and approximately 53% in Spain, studied by Malats *et al*, is responsible for severe functional loss of CFTR function. Three additional studies on the prevalence of an abnormal CFTR allele in AP have been published as full papers.[3 6 7] Pooling these four studies, one or two mutant CFTR alleles were detected in 9/217 (4.1%) patients with AP. But the detection rate varies between 0% and 8.5% depending on the sensitivity of the screening method to detect an abnormal CF allele in the corresponding population (53–94%). None of the studies revealed a positive association of the 5T allele with IP or AP. Compared with the general population, delta-F508 was significantly more frequent in British and US Caucasian, but not in Australian or Spanish AP patients.

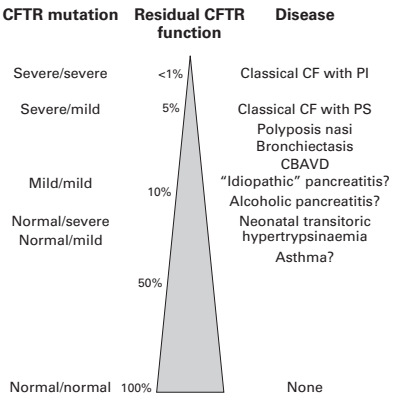

Figure 1 Disease manifestation according to residual cystic fibrosis transmembrane conductance regulator (CFTR) function as a result of the combination of severe or mild CFTR genotype. CF, cystic fibrosis; PS, pancreatic sufficiency; PI, pancreatic insufficiency; CBAVD, congenital absence of the vas deferens.

Up to now no environmental or genetic cofactor was identified in patients with mutant CFTR alleles associated IP, suggesting that impairment of CFTR function alone may be enough to induce pancreatitis.[1 2 3 8 9] On the other hand it may be speculated that patients with an abnormal CFTR allele, who develop pancreatitis in conjunction with alcohol abuse, may be characterised by a higher residual CFTR function, which by itself is not capable of inducing pancreatitis.

Therefore, to delineate the genetic background of pancreatic disease in AP it seems to be more appropriate to investigate the prevalence of uncommon mild variants ("atypical mutations") in large cohorts of AP patients than to test for the more common ("severe, typical") mutations of the CFTR gene in small patient groups. It has to be considered that the test kits for CFTR mutations often used in routine screening are usually designed to detect the more severe CF mutations. This would result in missing a substantial number of patients with milder CFTR mutations, as suggested by preliminary data on more comprehensive genetic testing in patients with ICP.[8]

J OCKENGA
Department of Gastroenterology, Medical School Jannover, 30625 Hannover, Germany

M STUHRMANN
Department of Human Genetics, Medical School Hannover, 30625 Hannover,Germany

M P MANNS
Department of Gastroenterology, Medical School Hannover, 30625 Hannover,Germany

Correspondence to: Dr J Ockenga.
Ockenga.Johann@mh-hannover.de

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Reply

EDITOR,—We agree with the view of Ockenga *et al* that from an ideal research perspective a complete analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene should be performed for cases of pancreatitis before a definitive statement on

the role of this gene in chronic pancreatitis can be made. However, it is well known that 18–30% of patients with CFTR related disorders (congenital bilateral absence of the vas deferens and bronchiectasis) have only one *CFTR* mutated allele.[1–3] Thus despite our study being based on only the two most common *CFTR* mutations (F508del and 5T), these two alterations should suffice to rule out or confirm a potential role of CFTR in patients with chronic pancreatic diseases. Furthermore, complete analysis of *CFTR* in the general population has led to the identification of amino acid variants of yet unknown functional significance in about 10% of subjects.[4] It is highly likely that complete analysis of *CFTR* would render a large number of amino acid changes of uncertain clinical and functional consequences, as it has been shown for patients with asthma.[5] As we proposed in our paper (*Gut* 2001;**48**:70–4), only the design of large studies specifically addressing these issues in target and adequate control populations and a comprehensive molecular analysis of *CFTR* will answer the question on the role of this gene in chronic pancreatic disease.

X ESTIVILL
T CASALS
Centre de Genètica Mèdica i Molecular-IRO, L'Hospitalet de Llobregat, Barcelona, Spain

N MALATS
M PORTA
Grup de Recerca d'Epidemiologia Clínica i Molecular del Càncer, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, Barcelona, Universitat Autònoma de Barcelona, Spain

L GUARNER
Servei de Digestiu, Hospital Vall d'Hebron, Barcelona, Spain

F X REAL
Unitat de Biologia Cel.lular i Molecular, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, Barcelona, Spain

Correspondence to Dr Malats.
nuria@imim.es

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Alcohol, obesity, and TNF-α

EDITOR,—The conclusions reached by Wigg *et al* (*Gut* 2001;**48**:206–11) about the origin and importance of tumour necrosis factor α (TNF-α) in non-alcoholic steatohepatitis (NASH) patients have failed to take into account the relationship between even modest alcohol consumption and TNF-α production and function. The authors found a lack of correlation between obesity and TNF-α levels in NASH patients and concluded that TNF-α, which they see as central to the pathogenesis of the condition, must have other sources.

We first described the strong correlation between obesity and serum TNF-α in 1998.[1] Adipose tissue synthesises a number of proinflammatory cytokines.[2] The negative correlation found in the Adelaide study is surprising given the findings in larger studies of non-NASH subjects and may be due to the small study numbers and not correcting for modest alcohol intake.

Alcohol consumption is considered a risk factor for the development and progression of liver disease in patients with fatty livers. We previously showed a strong negative correlation between any alcohol consumption and serum TNF-α levels in a general population sample. Modest alcohol consumption is known to suppress TNF-α production by monocytes, probably by suppressing post-transcriptional TNF-α production.[3] Furthermore, alcohol also has effects on TNF-α function mediated via high density lipoprotein (HDL). Alcohol enhances HDL levels by stimulating lipoprotein lipase activity in adipose tissue.[4] HDL not only inhibits TNF-α release from macrophages[5] but also protects certain cells against TNF-α induced damage.[6]

If TNF-α is important, then modest alcohol intake should be protective via suppression of TNF-α. This raises the possibility that TNF-α is not important in early steatohepatitis.

In defining patients with NASH, alcohol consumption must be rigorously excluded. In the Adelaide study, 10 of 22 patients drank up to 20 g of alcohol per day; however, even modest amounts of alcohol have effects on TNF-α levels and function.

The known interaction between alcohol and obesity in the pathogenesis of fatty liver and steatohepatitis suggests that investigators must look to factors other than TNF-α in studying the early pathogenesis of this condition. In the same way that altered cytokine homeostasis has been implicated in alcoholic liver disease, NASH is probably caused by changes to more than one proinflammatory cytokine. Interleukin 6 (IL-6) is a proinflammatory cytokine, a hepatocyte stimulating factor, and inhibitor of hepatic apoptosis. It has been suggested that hepatic steatosis is due to the rate of hepatocyte apoptosis becoming insufficient to match the rate of hepatocyte proliferation.[7] IL-6 induced liver regeneration may render the liver more susceptible to the effects of other insults. Unlike TNF-α, serum IL-6 exhibits a positive correlation with both obesity and alcohol intake (fig 1).[1 8] So far IL-6 has not been studied in the aetiology of NASH.

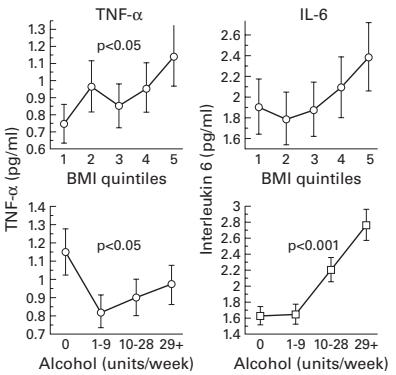

Figure 1 Relationship between the cytokines tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6), and obesity and alcohol. BMI, body mass index.

Future studies examining the link between TNF-α and NASH will need to rigorously control for alcohol consumption and assess many other aspects of the inflammatory cytokine network.

A POULLIS
M A MENDALL
Mayday University Hospital, Thornton Heath, Surrey, UK

Correspondence to: M A Mendall.
mike.mendall@mhc-tr.sthames.nhs.uk

1 Mendall MA, Patel P, Asante M, *et al.* Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart* 1997;**78**:273–7.
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Reply

EDITOR,—Our recent paper found increased small bowel bacterial overgrowth (50% versus 22%) and twofold increased systemic levels of tumour necrosis factor α (TNF-α) in patients with non-alcoholic steatohepatitis (NASH) compared with control age and sex matched subjects (*Gut* 2001;**48**:206–11). Poullis and Mendall question the finding of elevated TNF-α levels in blood in NASH subjects and quote their own work of elevated TNF-α levels in obese, male, middle aged subjects.[1] There was no correlation between TNF-α levels and obesity in our study whereas their study showed a correlation with obesity. How can this be explained? The question comes down to whether TNF-α is being produced predominantly in adipose tissue or in the liver, and which of these contributes to elevated systemic levels. At the moment this cannot be resolved. TNF-α will need to be investigated in liver biopsies and TNF-α levels sampled from the hepatic vein (not entirely impossible). The same should be done in animal models of obesity. In the meantime, it would be important to ascertain what proportion of obese patients have unrecognised NASH and whether this could explain the elevated TNF-α levels in obesity. Several lines of evidence suggest TNF-α is upregulated in the liver in alcoholic liver disease and presumably this is reflected by raised serum levels. We doubt therefore whether a low (<20 g/day) consumption of alcohol reduces systemic TNF-α levels but this could be formally studied. We have re-examined our data and found that there is no difference in mean TNF-α levels between those who

reported no alcohol consumption and those who drank alcohol. Finally, we would also comment from our recent work that shows that the C^{14}-D-xylose/H_2-CH_4 breath test is only positive in 60–69% of cases of small bowel bacterial overgrowth,[2] mostly because it depends on bacterial overgrowth being present on the day of testing. Thus small bowel overgrowth may have contributed even more to NASH than indicated in our paper.

A J WIGG
A G CUMMINS
Department of Gastroenterology and Hepatology, Queen Elizabeth Hospital, Woodville South, SA, Australia
and Department of Gastroenterology and Hepatology, Flinders Medical Centre, Bedford Park, SA, Australia

Correspondence to: Dr AJ Wigg, Department of Gastroenterology and Hepatology, Flinders Medical Centre, Bedford Park, SA 5042, Australia. alan.wigg@flinders.edu.au

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BOOK REVIEWS

Dyspepsia: The Clinical Consequences. Edited by V Heatley, P Moncur (£69.50). UK: Blackwell Science, 2000. ISBN 0-632-05458-1.

Dyspepsia is like pornography—everyone thinks they know what it is but no one can agree on a definition. This is where the analogy ends, however, as there are plenty of books on pornography but few have been written on dyspepsia compared with other areas of gastroenterology. Out of idle curiosity I searched the Internet for books on irritable bowel syndrome and found 25 published in the past five years compared with only three titles specifically on dyspepsia. This is surprising given that dyspepsia represents 50% of a gastroenterologist's workload and it is refreshing to see an up to date book on the subject.

The book discusses the epidemiology, pathophysiology, diagnosis, and treatment of dyspepsia in a methodical fashion. There are contributions from an illustrious list of authors many of whom have international reputations in the field of dyspepsia research. Each chapter acts as a well informed review on a particular aspect of dyspepsia. The editors and contributors are to be congratulated on ensuring each piece is authoritative yet relatively short and accessible. This approach means that the reader can dip into a chapter most relevant to them and receive up to date information on that topic.

If you read the book from cover to cover however the introductions to each chapter become somewhat repetitive. I became a little tired of hearing about the clinical importance of dyspepsia. There is a chapter on the definition of dyspepsia and yet five other chapters also define the condition. This can be confusing as some characterise dyspepsia as any symptom referable to the upper gastrointestinal tract whereas others take the more restrictive Rome II definition. The editors have taken a very broad definition of dyspepsia and have included chapters on gastro-oesophageal reflux disease. This will probably irritate some experts who believe reflux disease should be excluded. However, there is no diagnostic test for dyspepsia and therefore attempts at defining it become reminiscent of theological arguments about how many angels will fit on the point of a needle.

Another minor quibble is that there were only two chapters explicitly discussing *Helicobacter pylori* and dyspepsia. I realise that *H pylori* is only one of many causes of dyspepsia but given that this is one of the major discoveries in medicine over the past 20 years, more information on the organism might have been appropriate.

A more major criticism is that the book does not have a chapter that specifically discusses the management of dyspepsia. This is touched on in a few chapters but there are no firm conclusions reached and recent important trials in this area are not fully discussed. This book may therefore disappoint clinicians wanting a more didactic text on the evidence for the management of dyspepsia.

I would warmly recommend this book to all gastroenterologists with an interest in dyspepsia. This is a rapidly changing field which hopefully will be reflected in new editions of this work.

P MOAYYEDI

Nausea and Vomiting. Overview, Challenges, Practical Treatments and New Perspectives. RH Blum, WL Heinrichs, A Herxheimer (Pp 620; illustrated; £79.50/$135). Philadelphia: Whurr Publisher, 2000. ISBN 1-86156-079-6.

Nausea is an extraordinarily common and under appreciated symptom that afflicts patients and non-patients alike. In a North American population, approximately 15% of subjects surveyed had moderate to severe nausea in the past month. Thankfully, the nausea most of us experience is brief and self limited. Almost all of the medical and surgical subspecialties however have patients who are intermittently and chronically nauseated. Unfortunately, little progress has been made in the study of nausea from a pathophysiological and treatment viewpoint.

The authors of the book seek to change this situation and have produced a most interesting and readable book about nausea and vomiting for students, primary care physicians, and researchers interested in these unique human symptoms. Gastroenterologists with a clinical or research interest in nausea and vomiting will also find this book helpful in that it brings together a large amount of information that is not easily accessible to us.

The book is basically divided into three parts: in the first 14 chapters the relevant anatomy and physiology of nausea and vomiting, various research methodologies, therapeutics, relevant neuropeptides, and the economic impact of nausea and vomiting are covered. Next there are 18 chapters outlining "hands on" advice for diagnosing and treating the patient with nausea and vomiting. Finally, the last chapter in an excellent and extensive essay on nausea/vomiting as an evolutionary response of the ancient reptilian brain: the reptilian brain appears to be responding to an increasing number of nauseogenic precipitants created by our modern lifestyles, technologies, and therapeutics, as well as specific diseases/disorders. Why is this?

The authors raise many provocative issues. They reject the simplistic notion that nausea and vomiting are regularly activated as a response to a putative ingestion of toxic substances. This time honoured concept simply does not reflect the many situations where nausea and vomiting occur in the absence of toxic ingestants. Olfactory system stimuli are discussed in detail with regards to nausea and vomiting during pregnancy. The authors review an interesting concept that relates nausea and vomiting and gravity, as gravitational forces affect the basic organisation of brain function. Refreshing ideas and perspectives on nausea and vomiting are offered that encompass philosophy and psychology viewpoints, as well as physiology and pharmacology.

Nausea is more debilitating than vomiting. The authors argue that nausea should be clearly separated from vomiting in terms of studying pathophysiological mechanisms and developing therapies. Indeed, vomiting is the cure for nausea (at least temporarily)! Nausea is an "early warning system" evoked as the organism attempts to maintain homeostasis in response to the nauseogenic stimuli. Vomiting is described as an "accident" of cascading stimuli that ultimately overwhelm homeostasis and the inhibitory circuits that prevent the uncontrollable and potentially injurious vomiting reflex.

Gastroenterologists are not the only medical providers dealing with the problems of nausea and vomiting. "Nausea is in the air; nausea is everywhere" is a phase I often use when lecturing about the multidisciplinary problem of nausea and vomiting. The second major portion of the book incorporates 18 chapters in which a practical approach to the diagnosis and treatment of nausea and vomiting is described for many medical and surgical specialties. From allergy and immunology to gastroenterology, oncology, surgery, and sports and space medicine these chapters are an introduction to the treatment of nausea and vomiting by various specialists.

These chapters are a bit uneven in their thoroughness and somewhat redundant in that each specialty ultimately uses similar drugs and comfort techniques for their patients. The tremendous lack of progress in the therapy for nausea and vomiting makes this area an open field for drug and non-drug development.

The final chapter is an extensive essay on nausea and vomiting that encompasses stimulating paragraphs that are well worth reading for any student of nausea and vomiting symptoms. Topics range from the adaptive purpose of nausea as a warning sign of ongoing problems in the internal/external environment, as marshalling social support for the sufferer, and as a powerful stimulus for problem solving to avoid these symptoms in the future.

I highly recommend this book as thoughtful and thought provoking reading for anyone interested in the common and sometimes debilitating symptoms of nausea and vomiting. The authors provide excellent reviews and new insights that are now necessary to consider in the fight against nausea and vomiting.

K KOCH

Inflammatory Bowel Disease. D S Rampton, F Shanahan (Pp 108; illustrated; £12.00). Oxford UK: Health Press, 2000. ISBN 1-899541-49-7.

Would I feel tempted to buy this book? At £12.00 it is a give away price and an excellent buy. It provides an up to date and easily read guide to our present understanding of the cause, diagnosis, and management of Crohn's disease and ulcerative colitis. It certainly provides an authoritative handbook for specialist registrars or even concerned patients. Its one weakness lies in the absence of references—but within 100 pages could one realistically expect to achieve this? Its role as a handbook for a consultant is less clear. Most of the information it contains should be already known to him or her, but it certainly could refresh that knowledge.

Inflammatory bowel disease is laid out in an attractive format with clear subtitles, useful summary tables, and a good range of illustrations. The impact of inflammatory bowel disease on aspects of life such as fertility, sexual relations, education, employment, and the consequences of the disease in childhood are dealt with in a limited way. The growing role of the specialist nurse in counselling and support is not considered in the book although it could provide useful background reading for anyone working in such a role.

I was particularly impressed by the inclusion of such esoteric treatments as arsenic suppositories in the text although this was omitted from the index. Remicaide was also absent from the index but dealt with in the text. In future editions the index could be strengthened by a more uniform inclusion of key terms. Another useful innovation could be the listing of reliable web sites.

With the growth of expensive, lengthy, but definitive textbooks that are almost by definition out of date at the time of publication, there is a clear need for cheap authoritative works that will have a relatively short shelf life and can be quickly revised or replaced. The philosophy behind the Health Press gives hope that they may be able to fill this important niche in the medical book market. Critical to this approach is the need for low cost.

J F MAYBERRY

Practice of Therapeutic Endoscopy, 2nd edn. Edited by G N J Tytgat, M Classen, J D Waye, *et al* (Pp 328; illustrated; £99.95). Philadelphia: WB Saunders Co, 2000. ISBN 0702025615.

We are in the throes of a revolution in the printing world, the ramifications of which cannot be accurately foreseen but are certainly as likely to have as dramatic effect on global culture as did Johann Gutenberg's invention of printing in the 15th century. Maybe we should all be pleased that we are living right in the middle of the revolution in communications technology. It is an endless source of fascination to listen to those who just a few years ago could not distinguish a RAM from a ROM, now feeling free to wax lyrical to all within earshot about the latest bit of "state of the art" technology that they own. How good it is to be at the cutting edge of information technology.

Yet, maybe not everyone is head over heels in love with IT. While the medical and particularly the academic community are keen to grasp all the opportunities, there must be many publishers who are rather fearful about what the future might bring. For them, like for almost all of us, change brings uncertainty. But it is not good to question technological progress in the UK just now. We have a modernising government and its leader is fond of saying that he is proud of his country's past, but he does not want to live in it!

So what will modernisation bring to the publishing world. A whole generation is now being brought up to look upon the personal computer as the main means of communication. Conventional correspondence is now sneeringly dismissed as "snail mail". Maybe daily newspapers will hang in there a bit longer but what is the future of medical journals?

All of these thoughts were going through my mind as I read this book, the first edition of which was published six years ago. The sheer range of what can now be done interventionally through an endoscope is quite breathtaking. There is a series of essays on therapeutic endoscopy nearly all of which are of very high quality indeed. The publisher, WB Saunders, has served the editors very well. I think this book has been most beautifully produced—the illustrations are generally very fine and the reproduction of colour photographs is quite superb. This is a book that should be read by every trainee.

Yet there is a problem. It is something of a truism that medical textbooks are out of date before they are published. Of course that is always true, even in an area such as this where the pace of technological progress out speeds the publishing schedule. However, the problem here is rather deeper. In many ways, this book is a manual. It is full of helpful tips on "how to do it" and it is very good on pitfalls and how to avoid them. The problem is that the medium of a textbook just cannot be the way of the future for this sort of book. As most of the neologisms in the IT language, multimedia is a fairly ghastly word, nevertheless one just feels there ought to be a CD or DVD to go with the book.

Whether anybody will be publishing books like this in five years time is anyone's guess—but I wouldn't bet on it. Doubtless trees will be happier but in any case the present publishers state proudly in a preface that their policy is "to use paper manufactured from sustainable forests". Jolly good of them too!

I FORGACS

CORRECTIONS

An error occurred in the Science @lert article by Playford RJ (*Gut* 2001;**48**:594–5). The text and reference 1 should refer to the author "Kinzler" and not "Kinzlker". Professor Playford apologises for the incorrect spelling.

The authors of *Gut* 2001;**48**:816–20 have notified the journal of a computational error they made in figure 2. The correct figure is printed here. The one line of text that describes the figure, under the heading "intrahepatic cholangiocarcinoma" on p817, should now read, "There was, on average, a 12-fold increase in ASpMR per 100 000 population in ages 45 and above, with larger increases at older ages and in women (fig 2A, B)". The authors apologise for this error, and wish to point out that all the rest of the data are correct, and this does not change the findings reported upon in the paper or the interpretation.

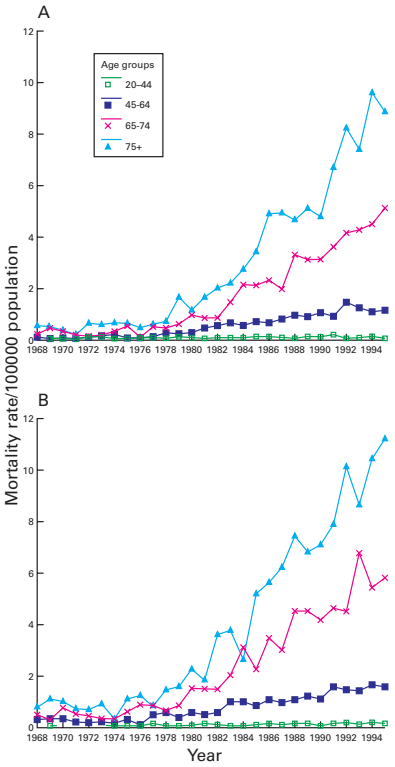

Figure 2 Age specific mortality rates per 100 000 population in England and Wales in (A) females and (B) males for intrahepatic cholangiocarcinoma.

NOTES

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2002

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2001 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in

March 2002. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Hopkins Endscopy Prize 2002

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2002. Applications (TEN COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Falk Symposium No 123: VI International Symposium on Inflammatory Bowel Diseases

This Falk Symposium will be held on 3–5 September 2001 in Istanbul, Turkey. Further information: Falk Foundation e.V. - Congress Division, Leinenweberstr. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 15 14 0; fax: +49 761 15 14 359; email: symposia@falkfoundation.de

Falk Symposium No 124: Medical Imaging in Gastroenterology and Hepatology

This Falk Symposium will be held on 28–29 September 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

9th Asian Conference on Diarrheal Diseases and Nutrition

This meeting will be held on 28–30 September 2001 in New Delhi, India. The organisers hope the meeting will promote meaningful and effective collaboration among individuals/institutions towards control of the major health problems in Asia, particularly those affecting women and children. Further information: Professor M K Bhan, Coordinator, Centre for Diarrheal Disease and Nutrition Research, All India Institute of Medical Sciences, New Delhi. Tel: +91 11 6963822; fax: +91 11 6862662; email: ascodd2001@rediffmail.com

VI Congress of the International Xenotransplantation Association

This congress will be held on 29 September to 3 October 2001 in Chicago, USA. Further information: Felicissimo & Associates Inc., 205 Viger Avenue West, Suite 201, Montreal, Quebec, Canada H2Z 1G2. Tel: +1 514 874 1998; fax: +1 514 874 1580; email: info@ixa2001chicago.com; website: www.ixa2001chicago.com

Falk Symposium No 125: Cytokines in Liver Injury and Repair

This Falk Symposium will be held on 30 September to 1 October 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

Falk Symposium No 126: Hepatocyte Transplantation

This Falk Symposium will be held on 2–3 October 2001 in Hannover, Germany. Further information: see Falk Symposium No 123 above.

EASL Single Topic Conference

The EASL Single Topic Conference "Liver fibrosis: from basic science to clinical targets" will be held on 12–13 October 2001 in Florence, Italy. Organisers: Massimo Pinzani (University of Florence) and Detlef Schuppan (University of Erlangen-Nuernberg). The aim of the conference is to provide the latest information on this key area of hepatology and to translate the current knowledge into clinical terms. It is directed at both the expert in the field and the general hepatologist. Further information: Massimo Pinzani, Dipartimento di Medicina Interna, Università degli Studi di Firenze, Viale GB Morgagni, 85, I-50134 Firenze, Italy. Tel: +39 055 4277845; fax: +44 39 055 417123; email: m.pinzani@dfc.unifi.it

Lecture Course in Coloproctology

This course will be held on 15–17 October 2001 in Harrow, UK. Professor Russell Stitz from Australia will be the Sir Alan Parks Visiting Professor and, for the first time, there will be a Sir Francis Avery Jones Visiting Professor, which will be Professor Paul Rutgeerts from Belgium. Further information: The Administrator, St Mark's Academic Institute, St Mark's Hospital, Northwick Park, Harrow, Middx, HA1 3UJ, UK. Tel: +44 (0)20 8235 4046/8; fax: +44 (0)20 8235 4039; email: stmarks@ic.ac.uk; website: www.stmarkshospital.org.uk

International Symposium on Hyperammonemia, Liver Failure and Hepatic Encephalopathy

This symposium will be held on 20–22 October 2001 in Valencia, Spain. Further information: Cátedra Santiago Grisolía, Fundación Museu de les Ciències Príncipe Felipe, Ciutat de les Arts i les Ciències, Avda. Instituto Obrero, s/n, 46013 Valencia, Spain. Tel: +34 96 197 44 66; fax: +34 96 197 44 70; email: catedrasg@cac.es.

ICGH-2: The Second Iranian Congress of Gastroenterology and Hepatology

The main Iranian meeting of gastroenterologists and researchers in this field will be held on 27 October to 1 November 2001 in Tehran, Iran. Further information: Dr Shahin Merat, Digestive Diseases Research Center, Shariati Hospital, N. Kargar Street, Tehran 14114, Iran. Tel: +98 911 717 3966; fax: +98 21 225 3635; email: merat@ams.ac.ir; website: www.ams.ac.ir/icgh.

Falk Symposium No 127: Autoimmune Diseases in Pediatric Gastroenterology

This Falk Symposium will be held on 8–9 November 2001 in Basel, Switzerland. Further information: see Falk Symposium No 123 above.

42nd Annual Conference of the Indian Society of Gastroenterology

This conference will be held on 23–29 November 2001 in Lucknow, India. The programme includes two pre-conference symposia (on gastrointestinal motility and scientific communication, on 23 November), a one day postgraduate course or CME (24 November), and an endoscopy workshop (28–29 November). Further information: Dr S R Naik, Department of Gastroenterology, SGPGI, Lucknow 226014, India. Tel: +91 522 440700 or 440800, ext 2400; fax: +91 522 440078 or 440017; website: www.sgpgi.ac.in/conf/isg2001.html

41st St Andrew's Day Festival Symposium on Therapeutics

This will be held on 6–7 December 2001 in Edinburgh, UK. Further information: Ms Eileen Strawn, Syposium Co-ordinator. Tel: +44 (0)131 225 7324; fax: +44 (0)131 220 4393; email: e.strawn@rcpe.ac.uk; website: www.rcpe.ac.uk

14th Intensive European Course of Digestive Endoscopy

This course will be held on 17–18 December 2001 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58; email: mail@m-centonze-conseil.com